Physicochemical Characterization of Poly(ethylene glycol) Plasticized Poly(methyl vinyl ether-*co*-maleic acid) Films

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ABSTRACT: The influence of the poly(ethylene glycol) (PEG) plasticizer content and molecular weight on the physicochemical properties of films cast from aqueous blends of poly(methyl vinyl ether-*co*-maleic acid) (PMVE/MA) was investigated with tensile mechanical testing, thermal analysis, and attenuated total reflectance/Fourier transform infrared spectroscopy. Unplasticized films and those containing high copolymer contents were very difficult to handle and proved difficult to test. PEG with a molecular weight of 200 Da was the most efficient plasticizer. However, films cast from aqueous blends containing 10% (w/w) PMVE/MA and either PEG 1000 or PEG 10,000 when the copolymer/plasticizer ratio was 4 : 3 and those cast from aqueous blends containing 15% (w/w) PMVE/MA and either PEG 1000 or PEG 10,000 when the copolymer/plasticizer ratio was 2 : 1 possessed mechanical properties most closely mimicking those of a formulation we have used clinically in photodynamic therapy. Importantly, we found previously that films cast from aqueous blends containing 10% (w/w) PMVE/MA performed rather poorly in the clinical setting, where uptake of moisture from patients' skin led to reversion of the formulation to a thick gel. Consequently, we are now investigating films cast from aqueous blends containing 15% (w/w) PMVE/MA and either PEG 1000 or PEG 10,000, where the copolymer/plasticizer ratio is 2 : 1, as possible Food and Drug Administration approved replacements for our current formulation, which must currently be used only on a named patient basis as its plasticizer, tripropylene glycol methyl ether, is not currently available in pharmaceutical grade. © 2009 Wiley Periodicals, Inc. J Appl Polym Sci 112: 2792–2799, 2009

Key words: adhesion; adhesives; drug delivery systems

INTRODUCTION

Poly(methyl vinyl ether-*co*-maleic anhydride) (PMVE/MAH) is a copolymer of methyl vinyl ether and maleic anhydride. This versatile copolymer has many applications, including use as a thickening agent, film former, dispersing agent, emulsion stabilizer, and denture adhesive.[1] Moreover, films cast from aqueous blends of PMVE/MAH are known to possess moisture-activated bioadhesive properties.[2] We have used such films previously as electrically conducting interfaces for bioelectrodes[3] and as an adhesive drug-delivery matrices.[4] Structurally, PMVE/MAH is a five-membered anhydride ring containing two carbon atoms in its backbone that confer rigidity on the system. On hydrolysis, the anhydride moiety is converted to its corresponding free acid form, poly(methyl vinyl ether-*co*-maleic acid) (PMVE/MA).

Films cast from aqueous blends of PMVE/MA are of little use as drug-delivery systems because of their very brittle nature. Therefore, they require the addition of a suitable plasticizer.[2] Plasticizers used for PMVE/MA film formulations are typically water-miscible polyhydric alcohols, such as glycerol.[5]

Research from our group has already demonstrated that a film cast from an aqueous blend containing PMVE/MA and the plasticizer tripropylene glycol methyl ether (TPME) possessed the necessary flexibility to make it ideally suited for conformation to the contours of the human body over extended periods of time.[2] Such a system was sufficiently flexible to conform to the contours of the vulva and facilitate normal ambulation when in place but of sufficient robustness to allow handling and manipulation.[6] Although TPME was effective in plasticizing PMVE/MA films,[2,6] it is not commercially available in pharmaceutical grade for drug-delivery applications. In fact, TPME is used as a solvent for stamp-pad inks and ballpoint and felt-tip writing pen inks, a coupling agent, a solvent in antirust paint, varnish removers, hard surface cleaners, and penetrating oils.[7] To date, we are the only research group to safely use TPME in clinical trials on a named patient basis with full ethical committee approval. The lack

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of availability of TPME in pharmaceutical grade has, however, prevented us from commercializing our formulation, despite excellent clinical results in the photodynamic therapy of vulval lesions.[8–11] Therefore, as an alternative to TPME in plasticizing PMVE/MA films, we investigated here, for the first time, the applicability of a Food and Drug Administration approved water-soluble polyhydric alcohol, poly(ethylene glycol) (PEG), to plasticizing PMVE/MA films.

EXPERIMENTAL

Materials

Gantrez AN-139, a copolymer of methyl vinyl ether and maleic anhydride (PMVE/MAH; weight-average molecular weight = 1,080,000 Da) was a gift from ISP Corp., Ltd. (Guildford, United Kingdom). PEGs with molecular weights of 200, 1000, and 10,000 Da were obtained from Sigma–Aldrich (Steinheim, Germany). Polyester film (a one-side siliconized, release liner; FL2000 PET 75 μ 1S) was obtained from Rexam Release B. V. (Apeldoom, The Netherlands). Glisseal N vacuum grease was purchased from Borer Chemie (Zuchwil, Switzerland). Resealable polyethylene bags (101 × 140 mm^2) were obtained from Agar Scientific (Essex, United Kingdom).

Methods

Preparation of the PMVE/MA–PEG films

Aqueous polymeric blends were prepared with the required weight of PMVE/MAH, which was added to ice-cooled water (reagent grade 1) and stirred vigorously to ensure complete wetting and prevention of aggregation. The mixture was then heated and maintained between 95 and 100°C until a clear solution was obtained. Upon cooling, the required amounts of PEGs with different molecular weights (200, 1000, and 10,000 Da) were added at 5, 10, 15, and 20% (w/w) in ratios of 4 : 1, 2 : 1, 4 : 3, and 1 : 1 (PMVE/MA:PEG), and the casting blend was adjusted to its final weight with water.

We prepared the films by slowly pouring the aqueous blend (30 g) into a mold consisting of a release liner (with the siliconized side up) secured to a Perspex base plate with a stainless steel clamp. Once assembled, the internal dimensions available for casting were 100 × 100 mm^2. The mold was placed on a leveled surface to allow the blend to spread evenly across the area of the mold. The cast blend was dried for 48 h at room temperature. After drying, the films were stored in resealable polyethylene bags.

Mechanical analysis

The mechanical properties of the formed films, namely, the tensile strength (τ), elongation at break [ε(%)], Young's modulus (YM), and work of failure (ω), were evaluated with a TA-XT2 texture analyzer (Stable Microsystems, Haslemere, United Kingdom) previously calibrated with a 2.0-kg load weight. The film thickness was determined with a digital micrometer (Hilka Pro-Craft, Hilka, Ltd., Surrey, United Kingdom) at six different points along the film, and the mean thickness was reported. The films were cut into strips of 50.0 × 5.0 mm^2 and grasped between upper and lower flat-faced metal grips surface-laminated with a smooth rubber for better hold. The initial distance between the grips was set at 15.0 mm, and this distance, therefore, represented the length of the film under stress. A crosshead speed (δ) of 6.0 mm/s was used for all measurements. The results were derived from the load–strain profile (Fig. 1),

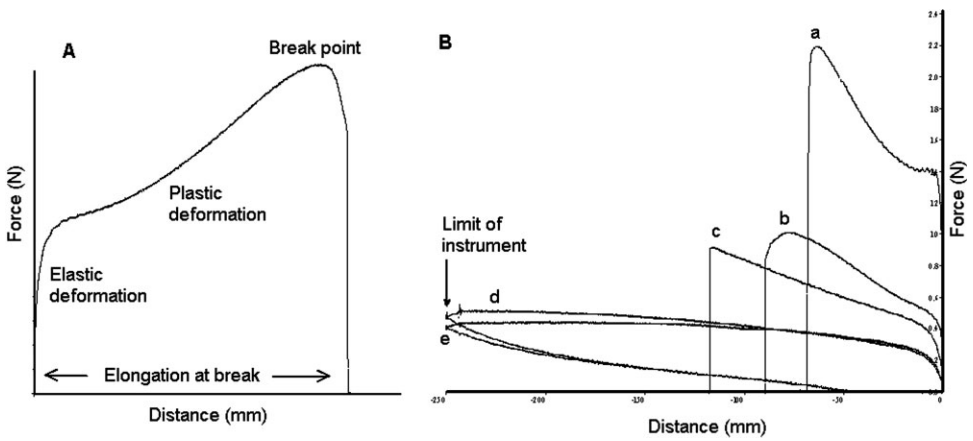

Figure 1 (A) Representative graph of the tensile stress–strain curve of a polymeric film. (B) Typical stress–strain profiles of plasticized PMVE/MA films obtained from texture analysis experiments: (a) 4 : 3 PMVE/MA 15% : PEG 10,000, (b) 4 : 3 PMVE/MA 15% : PEG 1000, (c) 4 : 3 PMVE/MA 15% : PEG 200, (d) 1 : 1 PMVE/MA 15% : PEG 200, and (e) 1 : 1 PMVE/MA 20% : PEG 200.

with propriety software (Dimension 3.7E) (Stable Microsystems, Haslemere, UK). Only results from films that were observed to break in the middle region of the test strip during testing were measured. All tests were carried out at ambient conditions of 22 ± 2°C and a relative humidity of 43 ± 2% (Hygrometer Testo 608-H1, Testo, Ltd., Hampshire, United Kingdom). The equations for the determination of the tensile properties of the films are given next:[12]

$$t = \frac{L_{\max}}{A_i} \quad (1)$$

$$\varepsilon = \frac{\Delta l_b}{li} \times 100 \quad (2)$$

$$\mathrm{YM} = dL/dm/A_i \quad (3)$$

$$\omega = \mathrm{AUC} \times \frac{\delta}{A_i} \quad (4)$$

where $L_{\max}$ is the maximum load, A_i is the initial cross-sectional area of the sample, l_i is the initial gauge length, Δl_b is the increase in the length at the breaking point, dL/dm is the slope of the linear portion of the elastic deformation, ω is a function of the work done in the breaking of a film specimen and is representative of film toughness,[12] and AUC is the area under the curve. The results were reported as the mean of six replicates for each film formulation.

Thermal analysis

The ability of PEG to plasticize films cast from aqueous blends of PMVE/MA was determined by differential scanning calorimetry (DSC). DSC studies of the PMVE/MA films were carried out with a DSC Q100 (TA Instruments, Surrey, United Kingdom). Sample weights of 5.0–10.0 mg were sealed in nonhermetic-type aluminum pans and ramped at a heating rate of 10.0°C/min in nitrogen at a flow rate of 50.0 mL/min. The DSC was calibrated with the melting temperature of indium (156.6°C). The glass-transition temperature (T_g) of the films was determined as the midspan temperature of the step change in the heat-capacity curve.

The percentage water content of the films was determined with a Q500 thermogravimetric analyzer (TA Instruments). Samples of 5.0–10.0 mg were heated from ambient temperature to 200.0°C at a heating rate of 5.0°C/min. Nitrogen flow rates of 40.0 mL/min (balance purge gas) and 60.0 mL/min (sample purge gas) were maintained for all samples. The data from both the DSC and thermogravimetric analysis experiments were analyzed with a TA Instruments Universal Analysis 2000, version 4.4A. At least three measurements were taken, and a mean was determined in each case.

Attenuated total reflectance/Fourier transform infrared (ATR–FTIR) spectroscopy studies

ATR–FTIR spectroscopy was also used for the study of polymer films. An Accutrac FT/IR-4100 Series (Jasco, Essex, UK) system equipped with MIRacle diamond ATR was used at room temperature. Polymer films of 1.0 cm^2 were clamped on the stage of the sample holder, which had its torque controlled to ensure repeatable and constant pressure on the sample. This was monitored on the digital display of a built-in force gauge, which measured true force on the sample. Results were recorded in the region of 4000.0–400.0 cm^{-1} at a scanning speed of 2.0 mm/s and a resolution of 4.0 cm^{-1}, and a gain of 8.0 was used for all samples.

Statistical analysis

Where appropriate, statistical analyses of the results were performed with a one-way analysis of variance, where $P < 0.05$ was taken to represent a statistically significant difference. When there was a statistically significant difference, post hoc Tukey's HSD multiple comparison tests were then performed. Statistical Package for the Social Sciences, SPSS 15 version 2.0 (SPSS, Inc., Chicago, IL), was used for all analyses.

RESULTS

The films cast from aqueous blends of PMVE/MA without plasticizer were brittle and could not be tested with the texture analyzer because of excessive stress on the instrument. Therefore, the plasticizers used in this study were necessary, even to produce films that were suitable for mechanical tests. As shown in Table I, the addition of plasticizer generally led to progressive increases in film thickness as plasticizer content was increased. For example, the mean thickness of unplasticized films cast from aqueous blends containing 20% (w/w) PMVE/MA was 0.61 mm, which was significantly lower ($P < 0.001$ in each case) than 20% (w/w) films plasticized with PEG 10,000 (1.56 mm), PEG 1000 (1.12 mm), and PEG 200 (0.86 mm), where the copolymer/plasticizer ratio was 1 : 1. In general, increasing the molecular weight of PEG also caused an increase in the thickness of the corresponding plasticized films. However, films without plasticizer also showed a progressive increase in thickness as copolymer content was increased. Films cast from blends containing 5% (w/w) PMVE/MA were much thinner than those cast from blends containing higher polymer content. As a result, handling

TABLE I
Influence of the PEG Molecular Weight and Loading on the Mechanical Properties (Mean ± Standard Deviation, $n = 6$)

Formulation	T (mm)	τ (N/mm^2)	ε (%)	YM (N/mm^2)	ω (N/s)
A. 5% (w/w) PMVE/MA films					
PMVE/MA 5%	0.14 ± 0.03	ND	ND	ND	ND
PMVE/MA 5% : PEG 10,000					
4 : 1	0.15 ± 0.02	ND	ND	ND	ND
2 : 1	0.16 ± 0.04	ND	ND	ND	ND
4 : 3	0.22 ± 0.03	ND	ND	ND	ND
1 : 1	0.24 ± 0.03	31.02 ± 2.57	478.43 ± 35.92	9.32 ± 2.21	9146.1 ± 644.01
PMVE/MA 5% : PEG 1000					
4 : 1	0.16 ± 0.01	ND	ND	ND	ND
2 : 1	0.18 ± 0.02	ND	ND	ND	ND
4 : 3	0.21 ± 0.03	58.05 ± 12.58	446.56 ± 50.99	21.41 ± 4.22	17746.31 ± 4150.80
1 : 1	0.25 ± 0.02	27.29 ± 4.81	603.76 ± 91.13	0.85 ± 0.44	2528.32 ± 432.14
PMVE/MA 5% : PEG 200					
4 : 1	0.16 ± 0.02	—	—	—	—
2 : 1	0.17 ± 0.02	105.95 ± 14.28	294.74 ± 141.6	50.37 ± 7.30	19210.74 ± 8538.67
4 : 3	0.20 ± 0.02	9.98 ± 2.43	758.59 ± 93.43	1.63 ± 0.48	3631.52 ± 1094.25
1 : 1	0.22 ± 0.02	2.21 ± 0.33	1238.32 ± 119.82	0.09 ± 0.05	1500.11 ± 312.59
B. 10% (w/w) PMVE/MA films					
PMVE/MA 10%	0.28 ± 0.03	ND	ND	ND	ND
PMVE/MA 10% : PEG 10,000					
4 : 1	0.50 ± 0.11	ND	ND	ND	ND
2 : 1	0.42 ± 0.01	85.98 ± 8.24	250.71 ± 134.99	38.20 ± 7.04	12756.89 ± 732.38
4 : 3	0.54 ± 0.10	8.82 ± 1.35	398.85 ± 100.42	5.92 ± 1.47	2865.75 ± 853.23
1 : 1	0.47 ± 0.01	4.34 ± 0.53	602.84 ± 97.51	1.35 ± 0.55	1593.14 ± 155.43
PMVE/MA 10% : PEG 1000					
4 : 1	0.33 ± 0.07	ND	ND	ND	ND
2 : 1	0.42 ± 0.02	46.34 ± 11.09	246.02 ± 137.48	24.06 ± 9.47	6954.13 ± 3406.10
4 : 3	0.47 ± 0.05	5.47 ± 0.67	493.05 ± 109.05	2.57 ± 0.97	1827.22 ± 307.65
1 : 1	0.49 ± 0.02	2.68 ± 0.31	786.52 ± 136.26	0.20 ± 0.07	1239.54 ± 341.72
PMVE/MA 10% : PEG 200					
4 : 1	0.31 ± 0.03	ND	ND	ND	ND
2 : 1	0.34 ± 0.05	9.96 ± 2.37	604.62 ± 93.34	2.72 ± 0.76	3498.26 ± 671.30
4 : 3	0.47 ± 0.02	2.68 ±0.64	699.80 ± 88.18	0.19 ± 0.09	1095.47 ± 311.71
1 : 1	0.57 ± 0.02	0.68 ± 0.13	1226.06 ± 241.84	0.04 ± 0.01	709.95 ± 139.24
C. 15% (w/w) PMVE/MA films					
PMVE/MA 15%	0.50 ± 0.03	ND	ND	ND	ND
PMVE/MA 15% : PEG 10,000					
4 : 1	0.55 ± 0.05	ND	ND	ND	ND
2 : 1	0.63 ± 0.02	31.60 ± 7.89	311.99 ± 116.12	21.19 ± 6.86	6168.27 ± 1813.68
4 : 3	0.66 ± 0.05	7.47 ± 0.74	462.73 ± 74.72	2.49 ± 1.11	2361.79 ± 292.66
1 : 1	0.80 ± 0.08	2.66 ± 0.67	718.31 ± 49.64	0.22 ± 0.11	1214.15 ± 262.05
PMVE/MA 15% : PEG 1000					
4 : 1	0.60 ± 0.05	ND	ND	ND	ND
2 : 1	0.71 ± 0.12	24.62 ± 12.69	252.78 ± 41.75	19.56 ± 8.65	5637.77 ± 1247.00
4 : 3	0.64 ± 0.04	3.74 ± 0.34	730.59 ± 94.36	1.36 ± 0.45	1033.10 ± 165.82
1 : 1	0.86 ± 0.05	1.35 ± 0.25	825.65 ± 89.39	0.14 ± 0.05	573.00 ± 109.00
PMVE/MA 15% : PEG 200					
4 : 1	0.57 ± 0.01	ND	ND	ND	ND
2 : 1	0.51 ± 0.06	14.53 ± 1.76	668.04 ± 34.19	1.15 ± 0.21	5379.54 ± 636.75
4 : 3	0.64 ± 0.01	3.90 ± 0.67	959.39 ± 101.58	0.12 ± 0.02	568.00 ± 39.00
1 : 1	0.76 ± 0.06	HE	HE	HE	HE
D. 20% (w/w) PMVE/MA films					
PMVE/MA 20%	0.61 ± 0.02	ND	ND	ND	ND
PMVE/MA 20% : PEG 10,000					
4 : 1	0.63 ± 0.11	73.62 ± 12.36	7.89 ± 1.07	85.67 ± 19.94	251.55 ± 89.93
2 : 1	0.89 ± 0.04	7.02 ± 0.60	495.11 ± 42.75	3.33 ± 1.53	2655.67 ± 199.21
4 : 3	1.40 ± 0.12	1.13 ± 0.14	772.34 ± 69.83	0.21 ± 0.28	1020.00 ± 147.95
1 : 1	1.56 ± 0.01	0.51 ± 0.05	1159.39 ± 74.84	0.03 ± 0.00	706.78 ± 50.21
PMVE/MA 20% : PEG 1000					
4 : 1	0.69 ± 0.07	40.72 ± 8.67	7.28 ± 1.31	52.35 ± 5.76	129.72 ± 55.16
2 : 1	0.78 ± 0.06	4.72 ± 0.47	529.25 ± 55.32	1.74 ± 0.31	1709.46 ± 292.02
4 : 3	0.96 ± 0.03	1.15 ± 0.09	730.97 ± 34.74	0.19 ± 0.04	653.00 ± 58.91
1 : 1	1.12 ± 0.02	0.86 ± 0.10	1518.36 ± 189.67	0.04 ± 0.01	506.36 ± 156.80
PMVE/MA 20% : PEG 200					
4 : 1	0.60 ± 0.03	20.14 ± 6.25	11.74 ± 2.64	49.71 ± 3.83	94.00 ± 41.00
2 : 1	0.73 ± 0.12	3.24 ± 1.05	673.18 ± 53.03	1.92 ± 0.79	1214.33 ± 110.00
4 : 3	0.85 ± 0.05	0.85 ± 0.35	1141.93 ± 57.32	0.11 ± 0.02	514.00 ± 85.00
1 : 1	0.86 ± 0.08	HE	HE	HE	HE

HE, high film elasticity; ND, not determined; T, thickness of film sample.

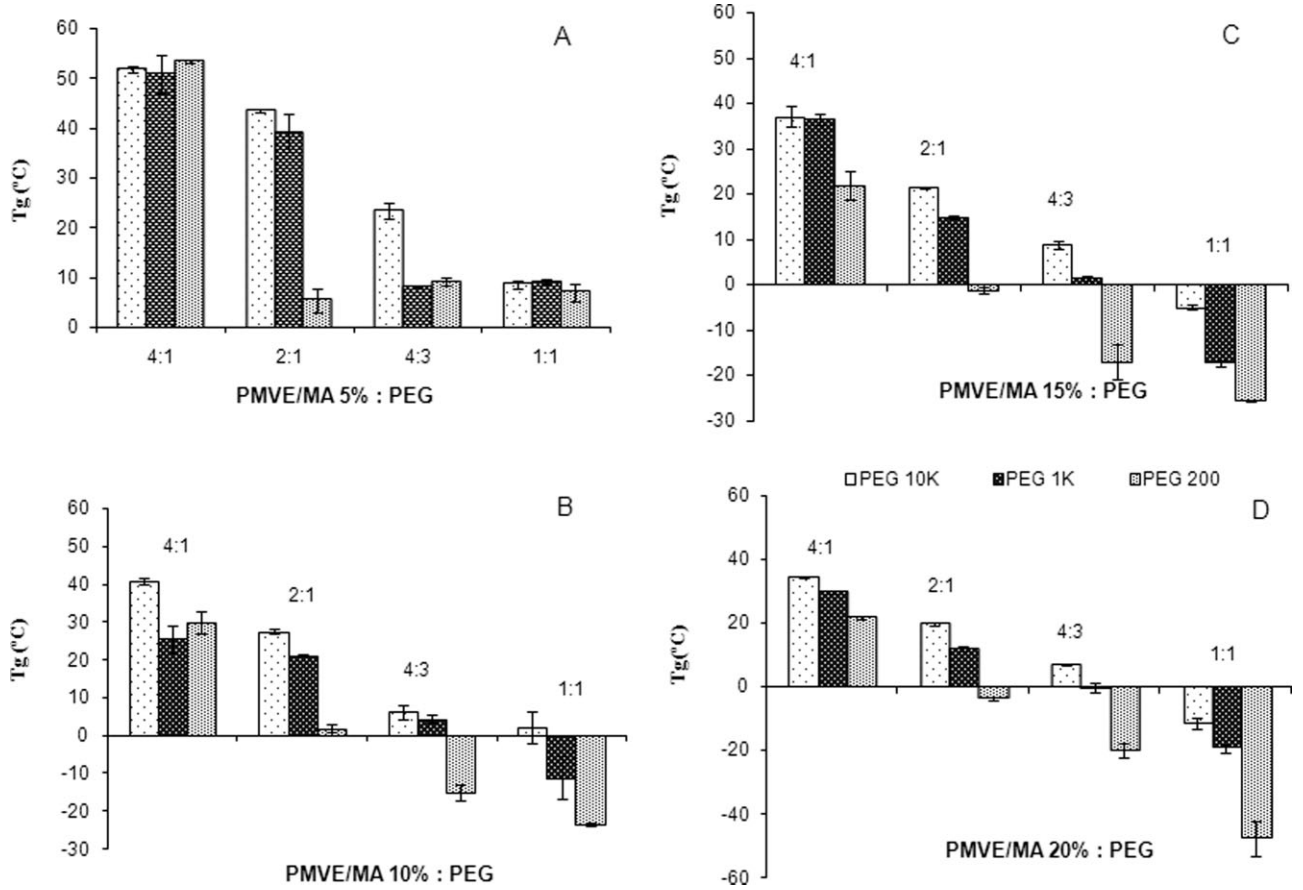

Figure 2 T_g values of a range of PEG-plasticized PMVE/MA films (mean ± standard deviation, n = 3).

of these films was problematic. In both cases, the increases in thickness observed were likely to be simply due to the addition of more material to the casting blends rather than to any other phenomena.

Table I shows the effect of the PEG molecular weight on the mechanical properties of the cast films. In general, increasing the concentration of PMVE/MA in the original casting blend, decreasing the PEG molecular weight, and increasing the PEG concentration all caused significant decreases in τ, YM, and ω and a significant increase in ε (%). For example, the mean τ's of films cast from aqueous blends containing 10% (w/w) PMVE/MA and PEG 10,000, PEG 1000, and PEG 200 where the copolymer/plasticizer ratio was 1 : 1 were 4.34, 2.68 and 0.68, respectively. In contrast, the same films showed a significant ($P < 0.001$ in each case) and progressive increase in ε (602.84, 786.52, and 1226.06%, respectively). Films cast from aqueous blends containing PMVE/MA (5, 10, and 15%) and PEG (10,000, 1000, and 200) where the copolymer/plasticizer ratio was 4 : 1 were very brittle and could not be tested. Films cast from blends containing PMVE/MA (15 and 20% w/w) and PEG 200 where the copolymer/plasticizer ratio was 1 : 1 were highly elastic in nature and also could not be tested. This is clearly evident in Figure 1, which shows that these films did not break even after they were extended by a distance of 250 mm, which was the limit of the instrument.

The T_g values of films cast from blends containing 5, 10, 15, and 20% (w/w) PMVE/MA without the addition of plasticizer were 52.17 ± 0.39, 51.57 ± 1.46, 52.39 ± 1.13, and 50.46 ± 1.26°C, respectively. Figure 2 shows the T_g values of plasticized PMVE/MA films. In general, T_g varied according to the film composition. The PEG molecular weight, PMVE/MA-to-PEG ratio, and PMVE/MA concentration in the original casting blend all influenced T_g. With respect to the PEG molecular weight, PEG 200 showed the largest drop in T_g, followed by PEG 1000 and PEG 10,000, compared to the unplasticized films. For example (Fig. 3), the T_g of films cast from blends containing 15% (w/w) PMVE/MA and PEG 10,000 in a 4 : 3 ratio was 9.75°C, which was significantly higher ($P < 0.001$) than those of corresponding films containing PEG 1000 (1.89°C) or PEG 200 (−17.47°C). With respect to the PMVE/MA-to-PEG ratios, 1 : 1 showed the largest reduction in T_g followed by 4 : 3, 2 : 1, and 4 : 1. As the PMVE/MA

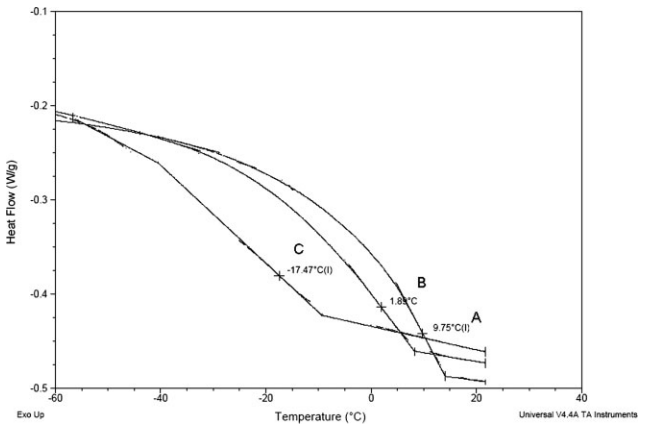

Figure 3 DSC heating thermograms of plasticized PMVE/MA films: (A) 4 : 3 PMVE/MA 15% : PEG 10,000, (B) 4 : 3 PMVE/MA 15% : PEG 1000, and (C) 4 : 3 PMVE/MA 15% : PEG 200.

concentration in the original casting blend was increased, T_g fell progressively.

The percentage water content of the PMVE/MA films at 5, 10, 15, and 20% (w/w) without the addition of a plasticizer was 16.91 ± 2.50, 16.28 ± 0.93, 15.69 ± 1.41, and 23.56 ± 0.52%, respectively. Figure 4 shows the water content of the plasticized films. Overall, the water content of the films varied between 11.7 and 23.7%. No statistically significant difference in water content was observed as the PMVE/MA content in the original casting blend was increased. Films containing PEG 200 where the copolymer/plasticizer ratio was 1 : 1 showed the highest water content in each case.

The ATR–FTIR spectra of the films cast from unplasticized 10% (w/w) blends of PMVE/MA and those cast from blends containing both 10% (w/w) PMVE/MA and PEGs were scanned in the region of 4000–600 cm^{-1}, as shown in Figure 5. A broad and intense hydroxyl region at 3497 cm^{-1} was observed for PMVE/MA, and the addition of PEG caused a shift in this band to lower wave numbers (3458, 3445, and 3411 cm^{-1} with the addition of PEG 10,000, PEG 1000, and PEG 200, respectively, where the copolymer/plasticizer ratio was 1 : 1). Table II shows the relative shifts in the ATR–FTIR spectra films cast from blends containing 10% (w/w) PMVE/MA. In the unplasticized films, the carbonyl stretching band was centered around 1704 cm^{-1}. With the addition of PEGs, shifts in the carbonyl stretching band were observed. Very similar ATR–FTIR results were observed when the other films investigated in this study were tested (data not shown).

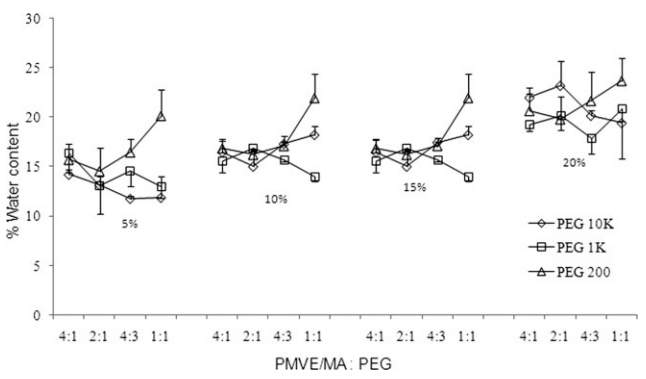

Figure 4 Water content (%) of a range of plasticized PMVE/MA films (mean ± standard deviation, n = 3).

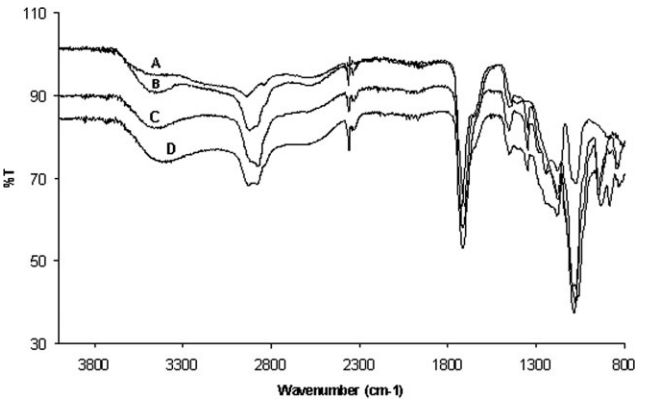

Figure 5 ATR–FTIR spectra of 10% (w/w) PMVE/MA films: (A) pure film, (B) film containing PEG 10,000 in a 1 : 1 ratio, (C) film containing PEG 1000 in a 1 : 1 ratio, and (D) film containing PEG 200 in a 1 : 1 ratio.

DISCUSSION

We previously showed plasticized PMVE/MA films to be very useful as drug-delivery platforms for a range of clinical applications.[2–4,8–11] In such instances, the flexibility, strength, and ability of such films to adhere strongly in moist environments have proven to be significant advantages over conventional pressure-sensitive adhesive-based devices. We have achieved notable clinical success with bioadhesive patches containing the photosensitizer precursor 5-aminolevulinic acid in matrices cast from aqueous blends containing 20% (w/w) PMVE/MA and 10% (w/w) of the plasticizer TPME.[6,8–11] The lack of availability of TPME in pharmaceutical grade has, however, prevented the wider use and commercialization of our patch. Consequently, in this study, we comprehensively investigated the plasticizing effects

TABLE II
Relative Shifts in the Hydroxyl and Carbonyl Regions of the ATR–FTIR Spectra for 10% (w/w) PMVE/MA Films Plasticized with PEG in a 1 : 1 Ratio

Formulation	Carboxyl stretching (cm^{-1})	Hydroxyl region (cm^{-1})
No plasticizer	1704	3497
PEG 10,000	1719	3458
PEG 1000	1724	3445
PEG 200	1718	3411

of a Food and Drug Administration approved plasticizer, PEG, on the mechanical properties of films cast from aqueous blends of PMVE/MA. The overall intention was to select candidate formulations that may be suitable for use as a component of a bioadhesive patch containing 5-aminolevulinic acid.

Polyhydric alcohols, such as propylene glycol, glycerol, and PEGs, are well known to be capable of acting as efficient plasticizers of PMVE/MA films.[13] However, to date, a comprehensive study such as this one investigating the influence of the PEG molecular weight and concentration in aqueous casting blends has not been performed. We found that unplasticized films and those cast from blends where the copolymer/plasticizer ratio was 4 : 1 were unsuitable for the formulation of a bioadhesive matrix for topical drug delivery because of their extremely brittle nature. This brittle behavior, as evidenced by tensile testing and T_g measurements, was suggestive of a high extent of interchain bonding within the three-dimensional structure formed after the polymeric films were dried. This was likely to be mostly due to polymer entanglements.[14]

In contrast, the addition of PEGs to the casting blends at copolymer/plasticizer ratios of 2 : 1 and 4 : 3 led to progressive softening of the formed films, such that τ, YM, ω, and T_g decreased significantly and ε (%) increased significantly. An increase in copolymer content for a given copolymer/plasticizer ratio had a similar effect. Films cast from blends where the copolymer/plasticizer ratio was 1 : 1 were extremely flexible and, as a result, difficult to handle. In fact, films cast from blends containing 15 and 20% (w/w) PMVE/MA and PEG 200 could not be tested with the texture analyzer because of excessive stress on the instrument. Films cast from blends containing 5% (w/w) PMVE/MA also caused difficulties during testing because of their extremely thin nature, which meant that handling was extremely problematic.

The plasticizing effect of polyols, such as PEG, can be attributed to their ability to interpolate between polymer molecules, bind water, and disrupt intermolecular polymer associations.[15] PEG 200 was the most efficient plasticizer of PMVE/MA followed by PEG 1000 and PEG 10,000. This can be explained by a smaller molecular volume and a relatively high number of hydroxyl groups per unit mass with decreasing molecular weight of the PEGs. Therefore, the low-molecular-weight PEGs may have diffused into and interacted more effectively with the PMVE/MA chains. This finding is consistent with other studies,[16–18] where various polymers were plasticized with PEGs of increasing molecular weight. Furthermore, it is also possible that the reduction in molecular weight increased the miscibility of PEG with the copolymer molecules, which may have resulted in further increases in plasticization efficiency.[18,19]

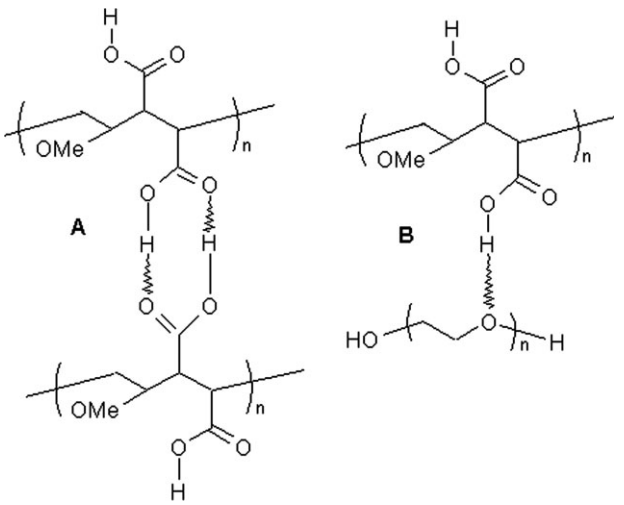

Figure 6 Possible hydrogen-bond interactions between (A) PMVE/MA and PMVE/MA molecules and (B) PEG and PMVE/MA molecules.

The water content of the films was not significantly affected by increasing polymer content. However, for films containing PEG 200, the water content increased progressively with increasing plasticizer content. Here, the plasticizers and polymer molecules bonded with water molecules and shielded active centers along polymer chains, which thereby decreased the number of intermolecular interactions and, thus, the rigidity of the three-dimensional structure formed upon drying.[20] Similar studies have reported water acting as a plasticizer of poly(vinyl alcohol) films.[21] Consequently, the water present in the PMVE/MA films may have acted as a synergistic plasticizer.

Shifts observed in the carbonyl stretching bands and in the hydroxyl region observed during ATR–FTIR suggested hydrogen-bond interactions between the PMVE/MA and PEG molecules in the plasticized films (Fig. 6). Hydrogen bonding may be within the same molecule (intramolecular hydrogen bonding) or, more likely, between neighboring molecules (intermolecular hydrogen bonding). Such interactions have been reported previously, where poly(ethylene oxide) forms hydrogen bonds with PMVE/MA, and hydrogen bonds form between PMVE/MA chains.[14] Notably, free hydroxyl groups usually absorb strongly in the 3650–3585-cm^{-1} region of the infrared region of the electromagnetic spectrum.[22] However, even in films cast from blends containing 10% (w/w) PMVE/MA and no plasticizer, the hydroxyl region was shifted to 3497 cm^{-1}. The general increase in the flexibility of the films observed with increasing polymer concentration was suggestive of the self-plasticizing effect of the polymer itself because of enhanced hydrogen-bonding interactions.[14]

Films cast from aqueous blends containing 10% (w/w) PMVE/MA and either PEG 1000 or PEG 10,000 when the copolymer/plasticizer ratio was 4 : 3 and those cast from aqueous blends containing 15% (w/w) PMVE/MA and either PEG 1000 or PEG 10,000 when the copolymer/plasticizer ratio was 2 : 1 possessed flexibilities, as evidenced by ε (%) values, most closely mimicking those of films cast from blends containing 20% (w/w) PMVE/MA and 10% (w/w) TPME (354%), as used in our clinical studies.[6,8–11] Significantly, however, the films prepared in this study had appreciably greater τ values than this formulation (2.65×10^6 N/m^2) in each case. This means that the films detailed previously possessed the requisite mechanical properties to allow good conformability to the contours of the human body, while being sufficiently robust to prevent damage during application and while in position.

We previously found that films cast from aqueous blends containing 10% (w/w) PMVE/MA performed rather poorly in the clinical setting, where the uptake of moisture from patients' skin led to reversion of the formulation to a thick gel, which oozed away from the site of application.[6] This was not observed for films cast from blends containing 15% (w/w) PMVE/MA. Consequently, we are now investigating films cast from aqueous blends containing 15% (w/w) PMVE/MA and either PEG 1000 or PEG 10,000 where the copolymer/plasticizer ratio is 2 : 1 as possible replacements for this formulation. We are studying the effects of 5-aminolevulinic acid incorporation on the mechanical and bioadhesive properties of these new formulations. Importantly, as we previously found that PMVE/MA can be crosslinked by polyols, such as glycerol, upon storage, with concomitant decreases in flexibility and bioadhesive capacity,[2] we are also investigating the long-term interactions between PEG and PMVE/MA.

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